Sounding Board

Are Research Ethics Bad for Our Mental Health?

PATIENTS with mental illness are much better off now than they were only a few decades ago. Diagnostic methods are more reliable, and treatments are more effective. Only a minority of psychiatric patients require long-term hospitalization, and the practice of psychiatry is now more like the practice of other medical specialties. At the same time, the prevalence of psychiatric disease is more clearly recognized. Five of the world's 10 leading causes of disability are psychiatric: depression, alcohol abuse, bipolar mood disorder, schizophrenia, and obsessive–compulsive disorder.[1] Each of these disorders has important genetic determinants and biologic correlates. In the past 40 years, specific effective treatments for each have replaced nonspecific concern and support.[2] We have developed pharmacologic agents for depression, mania, psychosis, obsessions, and panic, as well as agents that block the craving for drugs of abuse, calm hyperactive children, and slow the progress of Alzheimer's dementia. We have also developed psychological treatments for depression and methods of psychosocial management for patients with schizophrenia. This progress has been based on the immense growth of both basic and clinical psychiatric research. By 1995, academic departments of psychiatry were second only to departments of medicine in terms of funding for research.[3]

However, there has been concern about the ethical aspects of psychiatric research. Are mentally ill subjects especially vulnerable to exploitation? Are they competent to give informed consent? Are psychiatric research methods particularly dangerous? Are special procedures or regulations needed for such research? There have been attacks and defenses of psychiatric research in the courts, in the media, and in statements made by groups that advocate for the rights of the mentally ill.

Perhaps the most vexing ethical problem has concerned mentally ill patients who have a diminished capacity to consent to participate in research. The Nuremberg Code, formulated in 1947 as a result of the trial of Nazi physicians who had experimented on unwilling subjects, stated that "the voluntary consent of the human subject is absolutely essential."[4] Henry Beecher, a pioneer of research ethics, wrote in 1959 that this principle would "effectively cripple if not eliminate most research in the field of mental disease."[5] Society has struggled with this ethical dilemma ever since. There is agreement that research on human subjects requires informed consent but that, at the same time, we must learn as much as possible in order to improve the care of those who suffer from diseases that impair their capacity to provide informed consent. How do we proceed when these goals are in conflict, when conducting research on those who cannot themselves consent to participate in it is the route to improving their care?

In 1964, the Declaration of Helsinki softened the absolute ban of the Nuremberg Code by allowing the legal guardians of incompetent persons to provide consent on their behalf, at least for "therapeutic" research.[6] In 1974, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was created after the revelation of the exploitation of subjects in the Tuskegee study of syphilis, discussed the special problem of the use of vulnerable groups as research subjects. Its recommendations moved beyond both the Nuremberg Code and the Declaration of Helsinki. The commission argued that "prohibiting such research might harm the class of mentally infirm persons as a whole by depriving them of benefits they could have received if the research had proceeded."[7]

The commission suggested special regulations to govern research on "persons institutionalized as mentally infirm," but these regulations were viewed as overly burdensome and were never adopted. However, the commission's general comments paved the way for the so-called common rule. This is an executive order, first proposed in 1986 and issued in 1991, that governs the basic structure of regulations for research on human subjects conducted by the federal government or in facilities receiving federal funds.[8] The common rule recognizes the special problems of "vulnerable populations," including the mentally disabled. It requires that institutional review boards (IRBs) include additional safeguards to protect the rights of such groups[9] but provides no specific guidelines as to how IRBs should do so.

The National Bioethics Advisory Commission (NBAC) is the latest federal panel to address the issue. Its 17 members were appointed by President Bill Clinton in 1995 to advise the government on bioethical issues, and especially to "consider the problem of the rights and welfare of human research subjects." Its report was released in 1998.[10]

The NBAC reviewed judicial and public concerns about research on the mentally ill, including a 1992 lawsuit against the University of California at Los Angeles alleging that a research protocol involving a drug "washout" aggravated a patient's schizophrenic illness and led to his suicide.[11] (The university won in court, but its procedures were subsequently criticized by the Office for Protection from Research Risks of the National Institutes of Health. The patient's family has not permitted disclosure of the clinical data.) The NBAC also reviewed the series of judicial decisions in New York State that challenged regulations governing participation in research by persons who lack the capacity to give informed con-

sent,[12] and it reviewed media exposés (such as a recent series of articles in the *Boston Globe*[13]). The commission concluded that there were three justifications for its work: first, the perceived regulatory gap since the rejection of the recommendations of the earlier commission (although it did not find evidence that the current regulations governing IRBs are not effective); second, the apparently inadequate protection of human subjects in some cases (although the NBAC did not itself investigate such cases and did not find evidence of a "broken system"); and finally, the need to ensure public confidence in the research enterprise.

The ethical problems of research on the mentally ill seem somewhat different today from the way they did in the 1970s. The proposals rejected at that time referred to "persons institutionalized as mentally infirm," but today, clinical psychiatric research is performed largely in the outpatient setting. In the past, mentally ill persons were often viewed as broadly incompetent. Because of that view, their civil liberties were curtailed, and involuntary treatment was common. Today, there are few patients who are hospitalized against their will. Even those who are retain their rights, including their right to refuse treatment. Empirical studies suggest that impaired decision-making capacity may be less common among psychiatric patients (it is estimated to be present in about 52 percent of hospitalized patients with schizophrenia) and more common among those with serious medical illnesses (about 12 percent) than previously believed.[14,15] For example, a survey of patients with medical disorders found that 6 percent of those who believed they had never participated in medical research had actually done so, and 7 percent of those who had participated in research did not understand that they had the right to withdraw from it.[16]

The NBAC considered some of these changes, but nevertheless made the fundamental and highly controversial decision to focus its report on persons with mental disorders that may affect the capacity to make decisions rather than on all potential research subjects with actual or probable impaired capacity. In my view, this focus reflects the persistence of outmoded stereotypes. Psychiatric patients and psychiatric research are fundamentally similar to medical patients and medical research, respectively, and psychiatric patients should have the same rights, governed by the same safeguards and regulations, as those of medical patients. Regulations should be based on functional characteristics such as decision-making capacity rather than on diagnostic categories, particularly categories, such as mental illness, that have been subject to stigma.

The traditional definition of the capacity to consent to research requires that the subject understand the difference between treatment and research, the nature of the research being conducted, its risks and benefits, available alternatives, and the fact that he or she is making a decision and that the decision can be changed. The subject must not be swayed by a pathologic affective state, a false belief, or a dependent relationship that might interfere with the decision or with his or her autonomy and must be capable of making a stable, reasoned choice and communicating it. The NBAC agrees with this definition. Its most controversial recommendations concern the process of assessing the capacity to consent to research, the arrangements for surrogate decision making if this capacity is impaired, and the evaluation of the risks and benefits of research.

Currently, the capacity to consent to research is assessed in much the same way as the more familiar capacity to consent to treatment — that is, by the health care professionals and care givers who are closest to the patient. The NBAC would change this approach for all research involving more than minimal risk. The category of "more than minimal risk" is quite broad. It includes, for example, noninvasive magnetic resonance imaging (MRI) of the brain (because the noise, confinement, and apparatus could be distressing to a subject) or explicit questions about sexual preferences (which might upset a subject). Such research would require an assessment by an "independent qualified professional"; even the treating clinician would be disqualified from judging the capacity to consent to research if he or she were either participating in the research or employed by the institution conducting it. The NBAC considers the present system for evaluating a patient's capacity to consent to dangerous treatment inadequate even to assess the capacity to consent to MRI for research purposes. A similar proposal to use independent monitors of consent was a major factor in the rejection of the 1978 recommendations. Many psychiatric researchers consider these recommended procedures expensive, cumbersome, and clinically insensitive to the experience of impaired subjects, and some patient advocates fear that the implied mistrust of care givers may have a negative effect on the doctor–patient relationship.

For subjects found to have an impaired capacity to make decisions, the NBAC recommended acceptance of surrogate consent by legally authorized representatives, but with strict limits on their authority. Surrogate consent for research involving more than minimal risk (again, this includes brain imaging) would require approval of the protocol by a federal review panel, not just the IRB. This represents an extraordinary shift of authority from the community in which the research is being conducted to a central body distant from both the subjects and the researchers.

There are two problems with this suggestion. The first concerns what might seem to be a detail but turns out to be crucial. Similar regulations concerning children specify three levels of risk: "minimal risk," "minor increase over minimal risk," and "greater than minor increase over minimal risk." The middle category allows flexibility; there might not be

the same concern about an MRI or probing questions about sexual behavior (examples of a minor increase over minimal risk) that there would be about a muscle biopsy (an example of a greater than minor increase). The requirement that a federal panel review research involving only a minor increase over minimal risk will be a serious barrier to research that has been free of ethical difficulties, such as studies of psychosocial interventions designed to reduce high-risk sexual behavior in psychotic patients or to determine the value of brain imaging in elucidating the mechanism of action of psychotropic drugs.

The second problem relates to the NBAC's view not only that mental patients and psychiatric researchers are different from medical patients and medical researchers, but also that psychiatric research methods themselves entail special risks. The commission cites three such methods: challenge studies (such as the administration of ketamine, which causes transient increases in psychotic symptoms, to patients with schizophrenia), drug washouts or holidays (periods when drugs are withdrawn), and studies in which some patients receive placebos. The NBAC ignored the extensive literature on the actual risks of these research strategies (although in the week before its report was released to the public, the commission added a recommendation that the Institute of Medicine study the issue), but it nevertheless concluded that they "require special attention." Yet cardiac stress tests and glucose-tolerance tests are also challenge studies, drug-withdrawal strategies are commonly used in nonpsychiatric pharmacologic research, and placebo studies are often required by the Food and Drug Administration for drug approval. The risks of research may be small or large and it may be difficult to evaluate them, but there is nothing special about the evaluation of risk in psychiatric research as compared with other types of medical research.

The NBAC has made some excellent suggestions. One is that a federal panel collect data on the risks of various research interventions and the views of potential subjects. This will allow future guidelines to be based on facts rather than speculation and impressions. Another good suggestion is that funds be provided to cover the additional expenditures that the commission's recommendations would require. Oddly, the commission ignores the practical and ethical questions of who should provide these funds and what might have to be given up to make them available. Many psychiatrists and advocates for the mentally ill fear that the most likely result of adopting this recommendation will be a reduction in psychiatric research.

Finally, the NBAC suggests that IRBs that consider proposals involving persons with mental disorders should include members who represent the interests of the group being studied. This is a good principle. Unfortunately, it was not followed in the creation of the NBAC itself. Its 17 members include ethicists, scientists, physicians, patient advocates, and even an executive of a pharmaceutical company, but neither clinicians nor researchers in the fields of psychiatry or neurology. The New York[17] and Maryland[18] working groups that were studying the same issues at the same time made far less intrusive recommendations; each working group included at least 4 psychiatrists among its 13 or 17 members. The participation of psychiatrists might have ensured that the NBAC had a fuller understanding of contemporary psychiatric practice and research. Herbert Pardes, the psychiatrist who was chairman of the New York working group, has stated that as they stand, the NBAC recommendations would "set us back twenty years."[19]

The NBAC saw the absence of special guidelines for research involving mentally ill persons with impaired decision-making capacity as a "regulatory vacuum" and rushed to fill it. The absence of special regulations, however, does not necessarily define a vacuum, and providing additional regulations is not the best solution to all problems. The NBAC recognized that "unless individual investigators understand their ethical responsibilities no regulatory system will function properly" and quoted Henry Beecher, who observed that for human research subjects, "there is the more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator."[20] One danger of excessive regulations is that they can actually undermine researchers' sense of moral responsibility as their attention shifts from their obligation to research subjects to their compliance with the regulations.

The NBAC also justified its efforts by alluding to cases in which the protection of research subjects appeared to be inadequate. This is, of course, the most important justification; if protection has been inadequate in some cases, this problem should receive the highest priority. However, the commission did not determine whether research subjects have had inadequate protection. It would have been wise to find out how the current system is working and what problems exist before recommending new regulations to correct them — that is, to establish a diagnosis before prescribing a treatment.

Finally, the commission wanted to enhance public confidence in the psychiatric research enterprise. Singling out research on the mentally ill for special regulatory oversight, particularly in the context of media attention to unevaluated and unconfirmed allegations of abuse, is not likely to enhance public confidence.

Mentally ill persons with impaired decision-making capacity do not have one problem in regard to research ethics; they have two. The focus of the NBAC report is that the inability of such persons to provide full informed consent may leave them vulnerable to exploitation. The greater problem is that too little research is conducted on their behalf. Psychiatric research is burdened by a long history of public fear of mental illness, prejudice against the mentally ill, and distrust of those who treat or study

them. The methodologic problems of studying the brain and behavior and the clinical burdens of working with psychiatric patients have contributed to this problem in the past but are abating at present. It would be unfortunate if the NBAC's attempts to address the problem of impaired capacity not only were incomplete and ineffective but also had the unintended effect of impeding research on mental illness.

If the mentally ill are different in a way that raises questions about their civil liberties and prevents them from participating in research, and if psychiatric research is dangerous and researchers are not to be trusted, the strategy recommended by the NBAC has merit. On the other hand, if persons with psychiatric disorders are as able and entitled as those without such disorders to take part in and benefit from research, if creative researchers can design valuable, yet safe studies, if clinicians and researchers regularly place their research subjects' interests first, and if the public, patients, ethicists, researchers, and clinicians all share a common goal, then it is time to expand the dialogue and collect data about the strengths and weaknesses of the current system. We should search for solutions that will protect all persons who have impaired decision-making capacity without further stigmatizing the mentally ill, undermining the research agenda for mental illness, or diluting the moral responsibility of researchers.

ROBERT MICHELS, M.D.
Cornell University Medical College
New York, NY 10021

REFERENCES

1. World Health Organization. The global burden of disease. Cambridge, Mass.: Harvard University Press, 1997.
2. Michels R, Marzuk PM. Progress in psychiatry. N Engl J Med 1993; 329:552-60, 628-38.
3. Datagram: NIH extramural support to institutions of higher education by department. Psychiatr Rep 1995;10(2):19.
4. Trials of war criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Nuremberg, October 1946–April 1949. Vol. 2. Washington, D.C.: Government Printing Office, 1949:181-2.
5. Beecher HK. Experimentation in man. American lecture series publication no. 52. Springfield, Ill.: Charles C Thomas, 1959.
6. World Medical Association. Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. JAMA 1997;277:925-6.
7. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Report and recommendations: research involving those institutionalized as mentally infirm. Washington, D.C.: Government Printing Office, 1978:58.
8. Wolpe PR, Moreno J, Caplan AL. Ethical principles and history. In: Pincus HA, Lieberman JA, Ferris S, eds. Ethics in psychiatric research. Washington, D.C.: American Psychiatriac Association, 1999:11.
9. Protection of human subjects. In: Pincus HA, Lieberman JA, Ferris S, eds. Ethics in psychiatric research. Washington, D.C.: American Psychiatric Association, 1999:282.
10. Research involving persons with mental disorders that may affect decisionmaking capacity. Rockville, Md.: National Bioethics Advisory Commission, 1998.
11. Evaluation of human subject protections in schizophrenia research conducted by the University of California, Los Angeles, 1994. Bethesda, Md.: Office for Protection from Research Risks, 1994.
12. T.D., et al. v. New York State Office of Mental Health, et al., 626 N.Y.S. 2d 1015 (N.Y. Sup. Ct. 1995).
13. Kong D, Whitaker R. Doing harm: research on the mentally ill. Boston Globe. November 15–18, 1998:A1.
14. Appelbaum PS. Rethinking the conduct of psychiatric research. Arch Gen Psychiatry 1997;54:117-20.
15. Grisso T, Appelbaum PS. The MacArthur Treatment Competence Study. III. Abilities of patients to consent to psychiatric and medical treatments. Law Hum Behav 1995;19:149-74.
16. Sugarman J, Kass NE, Goodman SN, Perentesis P, Fernandes P, Faden RR. What patients say about medical research. IRB 1998;20(4):1-7.
17. New York State Department of Health Advisory Work Group on Human Subject Research Involving the Protected Classes. Recommendations on the oversight of human subject research involving the protected classes. Albany: New York State Department of Health, 1998.
18. Final report of the Attorney General's Working Group on Research Involving Decisionally Incapacitated Subjects. Baltimore: Office of the Maryland Attorney General, 1998.
19. Marshall E. Panel tightens rules on mental disorders. Science 1998; 282:1617.
20. Beecher HK. Ethics and clinical research. N Engl J Med 1966;274: 1354-60.

ETHICAL AND HUMAN-RIGHTS ISSUES IN RESEARCH ON MENTAL DISORDERS THAT MAY AFFECT DECISION-MAKING CAPACITY

FOR research with human subjects, the more things change, the more they remain the same. In the 50-odd years since the 10 principles of the Nuremberg Code were set forth by the U.S. judges who convicted the Nazi concentration-camp physicians of crimes against humanity, the tensions inherent in using human beings as a means to advance biomedical knowledge have surfaced repeatedly. Ever more detailed codes and regulations from governments as well as professional bodies, such as the World Medical Association in its oft-revised Declaration of Helsinki,[1] have not put the subject to rest. Indeed, the lesson of the past half-century is that suffering, death, and violation of human rights can arise not only when dictators give inhumane scientists free rein to treat human beings as guinea pigs,[2,3] but also when well-meaning physicians conduct research in a free and enlightened society.[4-6]

The most recent evidence of this phenomenon can be seen in two sets of problems: those associated with local supervision of research with human subjects in general and those that arise in psychiatric research, particularly that involving children and patients who are unable to make informed, voluntary decisions about their participation in such research. The two types of problems have come together in a number of instances, as investigators and institutions conducting research on mental disorders have been found by courts and federal bureaus, such as the Office for Protection from Research Risks at the National Institutes of Health, to have violated applicable statutes and regulations.

In a series of reports released in June 1998, the inspector general of the Department of Health and Human Services concluded that reforms were need-